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CASE REPORT

Getting the tissue is the issue?

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Abstract

A 65-year-old man presented to hospital with fever, abdominal pain and a central liver lesion on computed tomography. He was treated for a presumed liver abscess but despite antibiotic treatment there was progression of disease. A liver biopsy was eventually performed and showed a diffuse large B-cell lymphoma. By this time, the patient's condition had, however, already deteriorated to a point that additional treatment was no longer possible. Because obtaining a tissue sample is regularly hindered by fear of complications, we discuss the actual incidence of complications for liver biopsy.

Introduction

We present a patient with progressive multiorgan failure due to a presumed liver abscess despite antibiotic treatment. The eventual fatal outcome highlights the importance of an early tissue diagnosis. Even though this importance is often recognised, obtaining a tissue sample is hindered by fear of complications. We therefore also discuss the potential risks and actual incidence of complications for liver biopsy.

Case

A 65-year-old man was presented to a regional hospital with fever and abdominal pain. His previous history included Crohn's disease for which he took azathioprine. Computed tomography (*figure 1*, day 0) showed ileal induration and a presumed central liver abscess 3 cm in diameter. The lesion was deemed too high risk for needle biopsy and a combination of ceftriaxone and metronidazole was started empirically. Blood cultures remained negative. Based on the presence of diarrhoea with negative faecal PCRs for infectious causes and the ileal induration on prior abdominal imaging, an exacerbation of Crohn's disease was also diagnosed, for which prednisolone 40 mg once daily was initiated. Despite an initial improvement with the aforementioned therapy, the patient was readmitted three weeks later with recurrence of fever and clinical deterioration. Abdominal imaging showed an increase in the size of the known liver lesion. At this time haemodynamic instability was also observed, which responded to fluid resuscitation. Over the next couple of days, however, he developed acute kidney injury with oliguria, a progressive acidosis with a lactate up to 5 mmol/l and impending respiratory failure. Because of this progressive organ failure, the patient was transferred to our hospital and admitted to the intensive care unit. His antibiotic regimen was changed to piperacillin with tazobactam. Continuous renal replacement therapy was initiated. Repeat imaging showed an increase in size of the main liver lesion, now 6 cm in diameter. Furthermore, a number of smaller new lesions and thoracic and abdominal lymphadenopathy up to 2 cm in diameter were observed (*figure 1*, day 24). A liver biopsy was scheduled. Additional microbiological investigations were negative for *Entamoeba* and mycobacterial disease. Despite adequate systemic perfusion as assessed clinically and by echocardiography, the serum lactate increased to 8 mmol/l. The prothrombin time was mildly prolonged at 24 seconds, activated partial thromboplastin time was 48 seconds, clotting factor V was normal at 90% activity, total bilirubin was 38 µmol/l and ferritin 2865 µg/l. There were no signs of encephalopathy. The liver biopsy was performed without complications. During the next couple of days, however, the lactate continued to rise gradually to more than 15 mmol/l (upper limit of detection). A repeat abdominal scan showed a marked increase in size and number of the liver lesions (*figure 1*, day 29). The preliminary biopsy results were consistent with either a poorly differentiated carcinoma or lymphoma. Because of the multiorgan failure and rapid deterioration, chemotherapy was no longer an option. The patient died after withdrawal of life support. Post-mortem examination showed a diffuse large B-cell lymphoma (DLBCL) with hepatic and bone marrow infiltration.

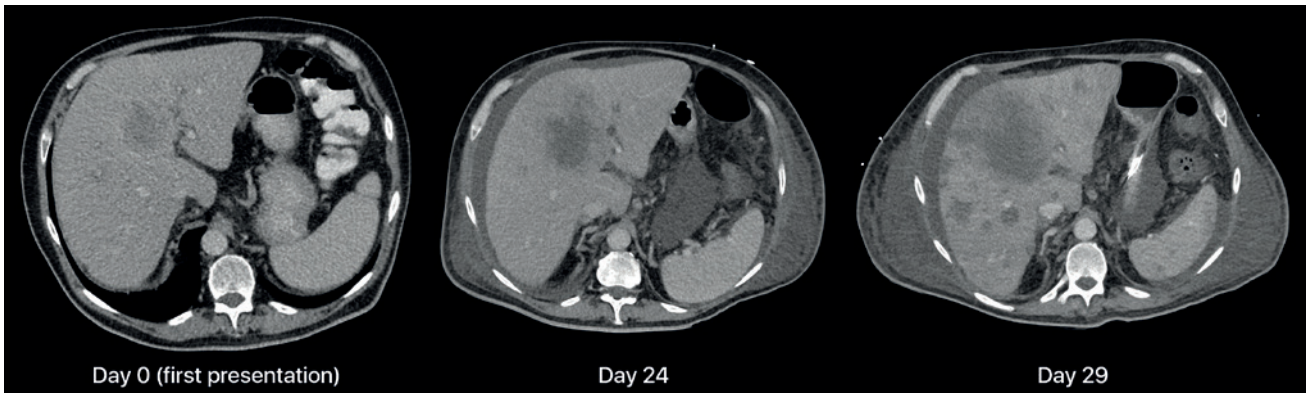

Figure 1. CT imaging at specified times during the course of the disease

Discussion

Tissue is the issue is a well-known adage in all of medicine, yet getting the tissue is often an issue of its own. In our case, because of the location of the abnormality and perceived high bleeding risk of a hepatic needle biopsy, it was initially decided to refrain from a biopsy and treat empirically for a presumed liver abscess.

After an initial slow progressive disease course, our patient developed a more rapid decline with features of systemic inflammation, acute kidney injury, hepatic dysfunction and respiratory failure. In hindsight, the systemic inflammation was likely caused by the fast growth of the lymphoma itself and its hepatic infiltration, as no infectious cause was identified during admission nor on post-mortem examination. We did not, however, determine an Epstein-Barr virus (EBV) viral load, so we cannot exclude EBV reactivation and proliferation in the setting of DLBCL. This could after all also explain the inflammatory response as EBV can cause marked inflammation even leading to haemophagocytic lymphohistiocytosis, for which this patient did meet some of the criteria. Although there were signs of some hepatic dysfunction and intrahepatic biliary obstruction early on, at that time there was no true hepatic failure as evidenced by the only mildly prolonged prothrombin time, normal factor V and absence of encephalopathy. We therefore suspected the elevated lactate to have been due to the Warburg effect, a phenomenon which occurs when malignant cells utilise the anaerobic glycolysis pathway as their main method of energy production despite adequate cellular oxygen availability. Unfortunately, however, by the time a definitive diagnosis was made, the patient had deteriorated beyond saving.

The initial diagnosis in our case was presumed to be infectious in origin. Although patients with Crohn's disease using immunosuppressants are at higher risk of infectious complications including liver abscesses, they are also at higher risk for malignant disease.[1] The initial favourable response to corticosteroids might have been due to temporary suppression of the lymphoma growth. This raises the point that since corticosteroids can cause transient improvement in many conditions, they can thereby mask the failure of other empiric therapies such as antibiotics in this case, obscuring a potential clue regarding misdiagnosis. Differentiating between an abscess and malignancy based on computed tomography is not always possible, with a reported specificity of 75% to 100% depending on the combined presence of multiple imaging characteristics.[2] Therefore, obtaining cytology or histology has obvious benefits in establishing a definitive diagnosis and in the case of an infectious cause, determining the pathogen and its susceptibility pattern.

Obviously, it is always important to weigh the potential risks of any treatment or procedure. Liver biopsy is a potentially high-risk procedure. However, a meta-analysis of 12,481 ultrasound-guided biopsies found an incidence of 0.9% for minor bleeding (i.e. no intervention needed), 0.4% for major bleeding (i.e. requiring transfusion or other intervention) and an incidence of 0.03% for pneumothorax.[3] Another recent single-centre retrospective study of 6613 image-guided liver biopsies showed platelets <50/nl to be a risk factor for post-biopsy haemorrhage with an incidence of 2.2% vs 0.5%, but not recent (i.e. within 10 days) aspirin or clopidogrel use or an INR >1.5.[4] Although the latter may appear strange, it is probably a reflection of the fact that a significant number of patients with an indication for a biopsy have liver function abnormalities resulting in derangement of both anticoagulant and procoagulant factors, and therefore the INR in isolation does not reflect in vivo haemostasis. Of note, the aforementioned studies do not specify detailed clinical characteristics of the included patients, but it can be assumed to largely consist of a non-intensive care unit population. We did not find data with regard to the complication rate of liver biopsy specific to the critically ill.

These data support the relative safety of a liver biopsy when performed by a trained physician. A more suitable test for

determination of the coagulation status in this setting might be thromboelastography, which could be helpful to perform a biopsy in the setting of a prolonged INR.[5] If the conventional percutaneous technique appears to be too risky, another option is a transjugular liver biopsy. Because of the endovascular nature of this procedure, any parenchymal bleeding will be diverted into the hepatic vein, though complications of course could still occur. In a review of 7469 transjugular liver biopsies, there were minor complications such as pain or neck haematoma in 6.6% of patients and major complications such as hepatic haematoma or intraperitoneal haemorrhage in 0.6%.[6] A significant disadvantage of this technique, however, is that it is impossible to target a specific site within the liver, making it of little to no practical value in more localised disease because of the high risk of sampling error.

In conclusion, even though liver biopsy has potential high-risk complications, the actual incidence of these complications is low and the negative consequences of missing a diagnosis are significant. Therefore, a biopsy should always be performed as soon as possible when there remains diagnostic uncertainty, especially in the face of clinical deterioration or radiological progression despite empiric treatment.

Disclosures

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Informed consent was obtained from the patient's relatives for the publication of this case report (and the accompanying images).

References

1. Fousekis FS, Theopistos VI, Katsanos KH, Tsianos EV, Christodoulou DK. Hepatobiliary Manifestations and Complications in Inflammatory Bowel Disease: A Review. Gastroenterol Res Pract. 2018;11:83-94.
2. Oh JG, Choi S-Y, Lee MH, et al. Differentiation of hepatic abscess from metastasis on contrast-enhanced dynamic computed tomography in patients with a history of extrahepatic malignancy: emphasis on dynamic change of arterial rim enhancement. Abdom Radiol (NY). 2019;44:529-38.
3. Tian G, Kong D, Jiang T, Li L. Complications After Percutaneous Ultrasound-Guided Liver Biopsy: A Systematic Review and Meta-analysis of a Population of More Than 12,000 Patients From 51 Cohort Studies. J Ultrasound Med. 2020;39:1355-65.
4. Boyum JH, Atwell TD, Schmit GD, et al. Incidence and Risk Factors for Adverse Events Related to Image-Guided Liver Biopsy. Mayo Clin Proc. 2016;91:329-35.
5. O'Leary JG, Greenberg CS, Patton HM, Caldwell SH. AGA Clinical Practice Update: Coagulation in Cirrhosis. Gastroenterology. 2019;157:34-43.e1.
6. Kalambokis G, Manousou P, Vibhakorn S, et al. Transjugular liver biopsy--indications, adequacy, quality of specimens, and complications--a systematic review. J Hepatol. 2007;47:284-94.